UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF LOUISIANA

In Re: TAXOTERE (DOCETAXEL) PRODUCTS LIABILITY LITIGATION

MDL NO. 2740

SECTION "H" (5)

THIS DOCUMENT RELATES TO: ALL CASES

MEMORANDUM IN REPLY TO DEFENDANTS' OPPOSITION TO PLAINTIFFS' MOTION TO PRESERVE EXPERT TESTIMONY

MAY IT PLEASE THE COURT:

Plaintiffs have provided a workable proposal that is a fair and efficient means of preserving general (not case specific) expert testimony for individual plaintiffs to use, if they so choose, as part of a trial package. Undersigned counsel are perplexed by the Defendants' claim that no "meaningful meet-and-confer" occurred when (1) an almost identical draft case management order was presented to the defendants as an attachment to an email from Mr. Miceli on January 19, 2021 requesting a meet-and-confer (after which multiple discussions were held prior to the filing of the motion); and (2) the issue was addressed in a status conference with the Court as an agenda item[1] for the February 19, 2021 lead/liaison zoom conference, at which each of the defendants' attorneys presented their concerns and/or objections to the PSC's proposed preservation of testimony CMO. Defendants' omission of these facts from their recitation of the history of this issue is, at best, an oversight; regardless, the claimed lack of a meaningful discussion is meritless.

Defendants' "vigorous" opposition is smoke and mirrors as it ignores the specifics of plaintiffs' proposal and, rather, focuses on case-specific matters that will appropriately be addressed with other case-specific experts or supplemental case-specific opinions. Plaintiffs have

[1] *See* Ex. 3, Joint Agenda for Lead/Liaison Conference, 02/19/2021.

not asked to take perpetuation depositions of any expert to opine on specifics of a case. To capitalize on the considerable efforts of counsel and the Court in this litigation, entry of Plaintiffs' proposed preservation CMO for non-plaintiff-specific expert testimony is an appropriate next step in the management of this MDL.

Defendants' claim of prejudice as a result of their intention to cross examine general causation experts on case-specific issues is inherently flawed and improper,[2] since those general experts do not opine on individual plaintiff issues.[3] Creative questioning, such as "Doctor, you did not see or evaluate the individual plaintiff to come to your conclusions in this case, did you?" or "You are not a dermatologist or dermatopathologist, are you?" or "Doctor, you don't treat, diagnose or evaluate hair loss, do you?" might solve the Defendants' issue. Moreover, the type of questioning that Defendants suggest is necessary (i.e., regarding side effects of other medications, varying dosages and regimens, and/or timing of use) are irrelevant to the question of general causation: can Taxotere cause PCIA. Defendants' concerns regarding side effects caused by other medications, to the extent they are relevant at all, are properly asked of eventual case-specific experts who will be disclosed in individual cases pursuant to future scheduling orders. These are case-specific issues, which should be addressed by the case-specific oncology expert, and they are not applicable to the proposed CMO.

Beyond the need to segregate Dr. Bosserman's case-specific portion of her prior reports out of the proposed preservation depositions, the remaining examples of why a single cross-examination would not be feasible are unpersuasive. Defendants have questioned Drs. Feigal,

[2] Questioning Dr. Madigan, for example, on why he did not meet with an individual plaintiff is improper under multiple Rules of Evidence, and particularly Rule 403, because it is irrelevant to his expert report and stated opinions in these cases.

[3] The only exception is Dr. Bosserman, whose opinions are separated into two parts: (1) general oncology issues, and (2) case-specific testimony regarding risk-benefit and options available to a specific plaintiff. The preserved testimony would only relate to general oncology issues. The other experts, Drs. Feigal, Madigan, Plunkett and Ross, each have testified they will not opine on case-specific issues.

Madigan, Plunkett, and Ross (and Kessler) extensively on consideration of case reports of other medications, lack of Bradford Hill analysis of other medications, and alternative causation issues. For general experts who do not opine on case-specific issues, such cross examination is not only feasible, but it has been done *ad nauseum* by counsel for three different defendants over multiple sittings with these witnesses.

With regard to the timing of a particular plaintiff's use of Taxotere and the related evolving state of medicine, knowledge and evidence, general causation is established without regard to timing. The trigger date for a regulatory obligation to update a label likewise will not change, although there will be testimony from Drs. Plunkett and Ross that the snowballing of evidence only grows stronger over time. For a future remanded trial case, the deposition testimony regarding this amalgamation of evidence in terms of the regulatory obligation could be cut in a manner that utilizes only the evidence that has amassed up to the point the plaintiff was administered Taxotere. However, the general opinion that some basis to believe a causal relationship existed such that the Taxotere label required an update to warn of permanent hair loss as early as in 2006 will not change from case to case.

Furthermore, any concern that a particular defendant is prejudiced by the preserved question-and-answer conducted by two questioning defense counsel could easily be remedied in particularized circumstances with a brief supplemental deposition for any issues a party can make a good faith showing were not covered in the deposition. Indeed, in the recent expert discovery of the *Kahn* matter, both Plaintiff and Sanofi agreed to adopt certain prior general expert reports and agreed, in such cases, that another deposition on the same prior report was not necessary. With regard to other experts, supplemental reports were issued on discrete topics and additional depositions were conducted based on the extent of the supplemental opinions. These types of

efficiencies are precisely the goal of MDL litigation to conserve resources and streamline pretrial proceedings.

Plaintiffs, who are cancer survivors with limited time left on this planet, are most prejudiced by the inefficiencies of not entering such a procedural mechanism to streamline expert discovery, and preserve testimony, in eventually remanded matters. And, the fact that science is evolving arguably could prejudice these plaintiffs more than defendants, as current science in a 2020 UpToDate acknowledges the risk of PCIA associated specifically with use of Taxotere and recommends that physicians specifically address this avoidable risk with their patients.[4] Such evolution in the science is no doubt a two-way street.

With regard to the concerns of the 505(b)(2) Defendants, Plaintiffs are somewhat confused by the suggestion that they are prejudiced. Sandoz and Accord have had a full opportunity to participate in expert discovery of Plaintiffs' general experts, and Hospira is scheduled to begin expert discovery for MDL Trial 5 next month. Plaintiffs' proposal does not supplant the pending bellwether trial expert work. Moreover, as discussed in the original supporting memorandum, each 505(b)(2) defendant, including the non-trial defendants, have attended, monitored and/or have access to the prior expert depositions conducted by Sanofi. The fact that rulings have not been made on certain 505(b)(2) *Daubert* briefing is of no moment. These experts previously accepted general causation opinions are not defendant-specific, rather they are specific to docetaxel and its propensity to cause PCIA. Future challenges to experts should be deferred to the transferor judges where remanded cases eventually are tried.

Concerning the "unavailability" issues raised by Defendants, it is interesting that defendants take such a position when Sanofi has taken the position that its own employees or

[4] *See* Ex. 4, H. Rugo, et al. "Alopecia related to systemic cancer therapy", *Wolters Kluwer: UpToDate, Inc.*, http://www.uptodate.com/contents/alopecia-related-to-systemic-cancer-therapy/print, 01/07/2020.

former employees, who are not adverse witnesses, are unavailable and whose deposition testimony may be played when the efficiencies of offering their witness only once in discovery for deposition benefits them (to avoid having to put him/her up at thousands of trials). It will be up to individual counsel whether they choose to use canned general expert testimony or not, and whether the transferor court will allow such testimony to be played. Those calls do not have to be made today; however, we know from experience (e.g., Dr. David Kessler) that some experts may become unavailable, and the likelihood of unavailability will increase over time. Thus, preserving this important testimony for potential future use is both an efficient use of resources and a proper part of a trial package formed through the efforts of the Plaintiffs' Steering Committee.

Regarding the procedural posture of this MDL, and the appropriateness of such a CMO at this stage of the proceedings, this MDL is nearing its fifth (5th) anniversary and general discovery as to four (4) defendants,[5] which represent more than 99% of the almost 10,000 known-PID cases. Doc. 12741 at 8. A bellwether case has been tried to verdict, and four sets of expert discovery have been completed involving three of those four defendants.[6] The PSC's proposed CMO is appropriate at this mature stage of the MDL for both efficiency purposes and to allow the PSC to meet its obligation in Pretrial Order No. 1 to prepare a trial package comprised of common pretrial materials.

Importantly, a model for just such a CMO has been established and demonstrated to work efficiently; in the PPA MDL, like this MDL, multiple manufacturers were named as defendants, yet the process of preservation depositions worked even where each defendant was not permitted to depose every general causation expert offered by the plaintiffs' leadership.[7] Similarly, not every

[5] Sanofi, Hospira/Pfizer, Sandoz, and Accord/McKesson.
[6] Expert discovery involving Hospira began in the *Sanford* bellwether matter but was suspended by agreement at the initial motions stage.
[7] *See* Rec. Doc. 12729-2, Ex. 1 to PSC's Motion to Preserve Expert Testimony.

plaintiff's counsel will be permitted to re-depose each of the Defendants' current and former employee witnesses.

For these reasons, and for those set forth in Plaintiffs' original supporting memorandum, the motion should be granted and Plaintiffs' proposed CMO should be entered to facilitate the preservation of general expert testimony as part of a trial package to be created by the PSC for use by individual plaintiffs' counsel, subject to eventual orders of transferor courts on their use/admissibility in remanded proceedings.

Dated: June 30, 2021

Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that on June 30, 2021, I electronically filed the foregoing with the Clerk of Court by using the CM/ECF system which will send a notice of electronic filing to all counsel of record who are CM/ECF participants.

/s/ M. Palmer Lambert
M. PALMER LAMBERT

EXHIBIT 3

Agenda for Lead/Liaison Conference

Taxotere MDL

February 19, 2021 (via Zoom)

1. Sanofi's Request for Supplemental Deposition of Dr. Kardinal in Kahn

   Sanofi requests the supplemental deposition of Dr. Kardinal. The parties are at an impasse and seek guidance on how to resolve this dispute.

2. Witnesses in the Kahn Trial

   Plaintiffs would like to discuss the possibility of calling remote witnesses during Ms. Kahn's trial. Defendants believe this topic is premature as no proposal has been made to Defendants nor has it been explained how any proposal would comply with the Federal Rules of Civil Procedure.

3. PSC Request for Entry of CMO on Preservation of Testimony for Trial Package

   The PSC requests entry of a CMO regarding preservation of expert testimony as part of their preparation of a trial package, as well as a date for the trial team to discuss issues with the Court. Defendants object to this request as inconsistent with MDL practice and restricting Defendants' due process rights. The parties seek guidance on the mechanism for resolution.

4. Trial 2A-5 Schedules

   The parties will provide a status of proposed adjustments to the trial schedules.

5. Trial 3 Oral Argument (March 18 and 19)

   Accord and Sandoz would like to address the status of in-person hearings at EDLA and whether the Court anticipates holding these hearings in-person or virtually. The parties have reached an agreement on the order of presentation of the remaining motions to be heard, and a proposed order of presentation has been submitted to the court.

EXHIBIT 4

Alopecia related to systemic cancer therapy

Authors: Hope S Rugo, MD, Mario E Lacouture, MD
Section Editors: Reed E Drews, MD, Maria Hordinsky, MD
Deputy Editor: Diane MF Savarese, MD

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: Aug 2020. | **This topic last updated:** Jan 07, 2020.

INTRODUCTION

Alopecia is a transient and usually (although not always) reversible consequence of systemic cancer therapy that can be psychologically and socially devastating [1]. For some patients, the emotional trauma may be so severe as to lead to refusing or delaying treatment that might otherwise be beneficial [2-8]. Recovery generally requires a period of several months to a year, amplifying the impact of the disease and its treatment.

A general overview of the anatomy and physiology of hair growth, the effects of systemic cancer therapies on the hair follicle, and possible means for preventing or minimizing alopecia are discussed here.

ANATOMY AND PHYSIOLOGY

The hair shaft is a layered structure that consists of three major components. The medulla, the innermost layer, is surrounded by the cortex and cuticle. The hair fiber is the product of the hair follicle, which is composed of three main parts when viewed in longitudinal section (figure 1) [9]:

- The lower portion, which extends from the base of the hair follicle to the insertion of the arrector pili muscle. This lower portion, in turn, is comprised of several major components:
  - The hair bulb, which contains the dermal papilla and hair matrix. The dermal papilla controls the number of matrix cells, which determines hair fiber size [10]. Melanocytes, which are responsible for hair color, are present among the matrix cells of the hair bulb.
  - The hair itself, consisting of medulla, cortex, and hair cuticle (inside to outside).
  - The inner root sheath, which consists of the inner root sheath cuticle, Huxley layer, and Henle layer (inside to outside). The inner root sheath is rigid, with its shape determining whether hair is curly or straight.
  - The outer root sheath.

  Damage to the lower portion of the hair follicle, as occurs in autoimmune alopecia areata, can result in a nonscarring alopecia. Immune-mediated alopecia areata can also be induced by immune checkpoint inhibitors that target cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death 1 (PD-1)/programmed cell death 1 ligand (PD-L1) [11]. (See "Evaluation and diagnosis of hair loss", section on 'Nonscarring alopecia' and "Toxicities associated with checkpoint inhibitor immunotherapy" and "Alopecia areata: Clinical manifestations and diagnosis".)

- The middle portion (isthmus), which extends from the insertion of the arrector pili muscle to the entrance of the sebaceous duct. This portion contains the "bulge" of the hair follicle, where the epithelial stem cells reside [12]. Damage to the bulge of the hair follicle results in irreversible scarring alopecia, as is seen clinically in disorders such as discoid lupus and lichen planopilaris.
- The upper portion (infundibulum), which extends from the entrance of the sebaceous duct to the follicular orifice.

Once formed, hair follicles undergo lifelong cycling characterized by periods of growth (anagen), regression (catagen), and rest (telogen), after which time the hair is shed (also known as exogen). Approximately 80 to 90 percent of follicles at any given time are in the active growth phase (anagen). During anagen, mitotically active matrix cells in the hair bulb differentiate and divide, resulting in a rate of hair growth of approximately 0.35 mm per day. Approximately 5 to 10 percent of follicles are in telogen (dormancy), during which all mitotic activity is arrested. The remaining 1 to 3 percent are in catagen, the involution phase. (See "Evaluation and diagnosis of hair loss", section on 'Hair cycle'.)

The final step of the hair cycle, exogen, is when the hair is released from the follicle. The scalp is estimated to contain on average 100,000 hairs, of which 100 to 150 are lost daily as part of the

normal hair cycle. This loss typically occurs after washing and brushing the hair, so patients who wash their hair less frequently may note a greater number of hairs falling out at each instance.

Multiple signaling molecules have been implicated in the initial development and subsequent cycling of the hair follicle, including Wnt, sonic hedgehog, notch, and bone morphogenic proteins, among others [13]. In a mouse model of chemotherapy-induced alopecia, transient overexpression of sonic hedgehog accelerated hair follicle regrowth [14].

EFFECTS OF CHEMOTHERAPY

Pathophysiology — Cytotoxic chemotherapy attacks rapidly dividing cells in the body, including the dividing hair matrix cells [15]. This can result in alopecia by one or both of two mechanisms (figure 2):

- If proliferation of the hair follicle matrix keratinocytes is severely inhibited, the hair may separate at the bulb and shed, a process referred to as anagen effluvium. Depending on the degree of toxicity on hair matrix keratinocytes, agents or schedules with lower toxicity will result in a dystrophic anagen effluvium, resulting in less alopecia and delayed hair regrowth; conversely, agents with greater toxicity will lead to severe alopecia but possibly more rapid hair regrowth [15]. (See "Evaluation and diagnosis of hair loss", section on 'Nonscarring alopecia'.)

- Thinning of the hair shaft can occur at the time of maximal chemotherapy effect, resulting in Pohl-Pinkus constrictions. As a result, the hair shaft may break at the follicular orifice during the resting phase of the hair cycle. (See "Evaluation and diagnosis of hair loss", section on 'Trichoscopy'.)

Reversibility of alopecia is related to the degree of damage to the hair follicle stem cells [15]. Because chemotherapy effects are typically specific for proliferating cells, which reside in the bulb, sparing the quiescent stem cells in the bulge (figure 1) that are responsible for reinitiating follicle growth, alopecia from chemotherapy is usually, but not always, completely reversible. (See 'Recovery and reversibility' below.)

Clinical characteristics — The term alopecia refers to the partial or complete absence of hair from any area of normal hair growth within the body. Chemotherapy-induced alopecia is most prominent on the scalp, with a predilection for areas with low total hair densities, in particular the crown and frontal areas of the scalp [16,17], where there is slower hair recovery. Total scalp alopecia is most common, but alopecia can also be diffuse or patchy.

Loss of eyebrows and eyelashes (madarosis), as well as axillary and pubic hair, is variable, and may even occur after the last dose of chemotherapy has been administered. However, recovery is generally more rapid for hair in these areas than for hair on the scalp.

The timing of alopecia depends on the type(s) of chemotherapy agents, dose, and schedule. For most regimens that are given every two to three weeks, alopecia starts around two weeks and is completely lost by the end of the second cycle of chemotherapy. Weekly chemotherapy generally results in slower and occasionally incomplete alopecia, and hair may actually start to grow back with continuing treatment. High-dose chemotherapy used in the setting of hematopoietic cell transplantation leads to rapid and complete alopecia [18].

Some chemotherapy agents may cause prolonged or permanent alopecia, most notably docetaxel given at doses of 75 mg/m^2 or higher per cycle, and less commonly paclitaxel [19-24]. In one prospective study of 61 patients treated for breast cancer, the proportion of participants who had permanent chemotherapy-induced alopecia at six months and three years was 39.5 and 42.3 percent, respectively [23]. Most cases involved incomplete hair regrowth. The effect is clearly dose and schedule related. It is important to advise patients about this risk before starting treatment with a specific regimen, as treatment alternatives may be available if patients are distressed by the possibility of permanent alopecia. (See 'Recovery and reversibility' below.)

Chemotherapy and targeted biologic agents may have effects on the hair other than alopecia:

- Methotrexate and some targeted biologic agents may temporarily affect the follicle melanocytes, inducing hyperpigmentation of scalp hair, eyebrow hair, and eyelashes; this tends to occur in bands that alternate with the normal color, a feature known as the "flag sign." This results from alternating periods of treatment and no treatment. (See "Cutaneous side effects of conventional chemotherapy agents", section on 'Hair'.)

- Small molecule inhibitors and monoclonal antibodies targeting epidermal growth factor receptor (EGFR), BRAF, Bruton tyrosine kinase (BTK), Bcr/Abl, cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), programmed cell death 1 (PD-1)/programmed cell death 1 ligand (PD-L1), KIT, and platelet-derived growth factor receptor (PDGFR)/vascular endothelial growth factor receptor (VEGFR) may result in hair curling and discoloration [11,25]. (See "Cutaneous adverse events of molecularly targeted therapy and other biologic agents used for cancer therapy", section on 'Other reactions'.)

- Additional agents may cause hair thinning without complete alopecia, including targeted biologic agents, antibody-drug conjugates, and standard endocrine therapy (particularly aromatase inhibitors) used in the adjuvant or metastatic setting [26]. Hair thinning with adjuvant endocrine therapy for early stage breast cancer has been associated with poorer compliance with therapy [27].

Quantitation — An alopecia grading scale for treatment-related alopecia is provided in the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) (table 1). In

addition, the psychosocial impact of alopecia on patients may be qualified using the Patient-Reported Outcomes (PRO)-CTCAE scale (table 2) [28] and the Chemotherapy-induced Alopecia Distress Scale (CADS) [29]. A more detailed grading scale used to assess the effectiveness of alopecia prevention strategies was developed by Dean and is referred to as the Dean Scale (table 3) [30,31]. Although this scale has not been independently validated in cancer patients, it is widely used.

Risk factors — The ability of chemotherapy agents to cause alopecia depends on the specific agent and the route, dose, and schedule of drug administration.

- Risk differs substantially between chemotherapy agents, with a number of agents causing little to no alopecia (table 4).
- High-dose, intermittent, intravenous chemotherapy regimens are associated with a high incidence of grade 2 (complete or total) alopecia.
- Low-dose therapy, oral administration, and weekly intravenous regimens are less likely to induce grade 2 alopecia [2,3]. As an example, every-three-week, high- or moderate-dose, intravenous cyclophosphamide almost universally causes alopecia, while oral cyclophosphamide-containing regimens are less likely to do so. However, some weekly therapies cause grade 2 alopecia in most patients (eg, eribulin).
- Combination chemotherapy regimens including drugs that cause at least some degree of alopecia are more likely to result in alopecia than single agents, depending, of course, on the agents and dose. The incidence of alopecia with common regimens has been inconsistently documented in the literature. (See "Acute side effects of adjuvant chemotherapy for early-stage breast cancer".)
- A retrospective, case-control genome-wide association study (GWAS) of DNA samples from breast cancer patients treated with chemotherapy suggested that the single-nucleotide polymorphism rs3820706 in calcium channel voltage-dependent subunit beta 4 (*CACNB4*) on 2q23 (among others) was significantly associated with chemotherapy-induced complete alopecia (odds ratio 3.71, $p = 8.13 \times 10^{-9}$) [32]. This suggestion of individual risk assessment is intriguing but would require validation in a prospective trial given the very high rates of complete alopecia reported with standard chemotherapy for breast cancer.

Concomitant factors that can affect the risk and extent of chemotherapy-induced alopecia include poor drug metabolism (eg, patients with liver dysfunction may have unexpected, significant alopecia), prior exposure to scalp irradiation, older age, the presence of androgenic alopecia, use of prior chemotherapy causing alopecia, and the presence of graft-versus-host disease in those patients who have undergone hematopoietic cell transplantation [15,33,34]. In contrast, hair type, ethnicity, and

race have not been associated with variations in either the extent of alopecia or the speed/pattern of hair regrowth. (See "Female pattern hair loss (androgenetic alopecia in women): Pathogenesis, clinical features, and diagnosis" and "Androgenetic alopecia in men: Pathogenesis, clinical features, and diagnosis".)

Agents with highest risk

Conventional cytotoxic agents — Of the commonly used intravenous single cytotoxic agents, those most likely to cause complete alopecia (dose and schedule dependent) include alkylating agents (cyclophosphamide, ifosfamide, busulfan, thiotepa), antitumor antibiotics (dactinomycin, doxorubicin, idarubicin), antimicrotubule agents (paclitaxel, docetaxel, epirubicin, ixabepilone, eribulin), and topoisomerase inhibitors (etoposide, irinotecan) (table 4). Alopecia is less common or incomplete with bleomycin, low-dose epirubicin or doxorubicin (especially <30 mg/m^2), oral cyclophosphamide, fluorouracil, gemcitabine, melphalan, methotrexate, mitomycin C, mitoxantrone, the platinums (oxaliplatin, cisplatin, and carboplatin), topotecan, and the vinca alkaloids. Antibody-drug conjugates are also associated with variable hair loss, which is agent specific.

Molecularly targeted agents — Small molecule inhibitors of EGFR, as well as monoclonal antibodies targeting EGFR, can induce a constellation of cutaneous symptoms, which include an acneiform rash, abnormal hair growth, pruritus, and dry skin; together, this symptom complex is referred to by the acronym PRIDE (papulopustules and/or paronychia, regulatory abnormalities of hair growth, itching, dryness due to EGFR inhibitors). (See "Cutaneous adverse events of molecularly targeted therapy and other biologic agents used for cancer therapy", section on 'EGFR inhibitors'.)

In addition, diffuse or partial alopecia may occur with a number of targeted agents [25]:

- The alopecia associated with agents that target EGFR is typically nonscarring and, therefore, reversible. However, anecdotal reports describe patients on long-term therapy who developed scarring alopecia [35,36], likely as a result of follicular and scalp skin infection. Interestingly, mice with a targeted deletion in EGFR gradually develop scarring alopecia [37].

- Reversible alopecia is also described in patients receiving treatment with orally active multitargeted tyrosine kinase inhibitors (with wide variations in incidence), such as the KIT/PDGFRA inhibitor ripretinib (approximately 50 percent), VEGF inhibitors sorafenib (approximately 29 percent), regorafenib (approximately 24 percent), cabozantinib (approximately 16 percent), pazopanib (approximately 12 percent), axitinib (approximately 8 percent), sunitinib (approximately 7 percent), vandetanib (not reported); the BRAF inhibitors vemurafenib (approximately 24 percent), dabrafenib (approximately 19 percent), and encorafenib (approximately 14 percent); and the Bcr/Abl inhibitors nilotinib (approximately 16 percent), dasatinib (approximately 8 percent), and imatinib (approximately 7 percent) [25,38-43].

- Alopecia is reported in 57 percent of patients treated with vismodegib, an orally active agent approved for advanced basal cell cancer that inhibits sonic hedgehog signaling [44]. It is less common (approximately 49 percent) with the related agent sonidegib, also approved for advanced basal cell cancer [45], and it is even less common (approximately 30 percent) in patients treated with the related agent glasdegib, which is approved for acute leukemia in older adult patients [46]. (See "Systemic treatment of advanced cutaneous squamous and basal cell carcinomas", section on 'Vismodegib'.)

- A new class of targeted agents, termed cyclin-dependent kinase (CDK) 4/6 inhibitors, has demonstrated marked efficacy in combination with endocrine therapy in patients with metastatic hormone receptor-positive breast cancer. Three agents have regulatory approval: palbociclib, ribociclib, and abemaciclib. Given in combination with aromatase inhibitors, these agents increase all-grade and grade 2 alopecia compared with that observed with endocrine therapy alone. There is approximately a doubling of all-grade alopecia, from 10 to 16 percent to 25 to 33 percent, and approximately a 1.5 percent increased incidence of grade 2 alopecia [47,48]. This alopecia appears to be reversible and may be treated with topical minoxidil, although there are no data about its efficacy. (See 'Topical minoxidil' below and "Treatment approach to metastatic hormone receptor-positive, HER2-negative breast cancer: Endocrine therapy and targeted agents", section on 'Aromatase inhibitors plus CDK 4/6 inhibitors'.)

- Grade 1 alopecia is a common yet underreported adverse effect of estrogen antagonist therapies (such as tamoxifen) and aromatase inhibitors, and it is reversible with cessation of therapy [26,49,50]. Rates of grade 1 alopecia for aromatase inhibitors have been reported in the range of 10 to 16 percent [47,48].

Recovery and reversibility — Because chemotherapy effects are typically specific for proliferating cells, which reside in the bulb, sparing the quiescent stem cells in the bulge that are responsible for reinitiating follicle growth, alopecia from chemotherapy is usually reversible. The hair follicle resumes normal cycling within a few weeks of treatment cessation, and visible regrowth becomes apparent within three to six months. The new hair frequently has different characteristics from the original; 65 percent of patients experience a graying, curling, or straightening effect, which is likely due to differential effects of chemotherapy on hair follicle melanocytes and inner root sheath epithelia, and these effects often resolve over time [2].

Although permanent alopecia is uncommon after standard-dose chemotherapy, there is now convincing evidence of permanent or prolonged alopecia after standard-dose chemotherapy for breast cancer (particularly with docetaxel and clearly related to both dose per infusion and duration of exposure) [19,23,51-53]. There is one case series suggesting cases of delayed recovery with

paclitaxel, although this is uncommon with current dosing schedules [22]. (See 'Anatomy and physiology' above.)

The impact of alopecia and potential alternative chemotherapy approaches should be discussed with each patient **before** the initiation of therapy that may lead to alopecia. This preemptive approach is important for minimizing the emotional distress associated with hair loss. For patients with breast cancer who are receiving docetaxel at doses of 75 mg/m^2 or above per infusion, it is important to advise patients about the risk of prolonged or permanent alopecia. Scalp cooling may prevent permanent alopecia, although the data are limited [53].

PREVENTION OF ALOPECIA

Therapeutic approaches include physically decreasing the amount of drug delivered to the dividing hair bulb by reducing scalp blood flow, and pharmacologic or biologic interventions to block the effects of the chemotherapy on the hair follicle.

Scalp hypothermia (scalp cooling) — Scalp cooling has been used extensively outside of the United States. Two automated scalp cooling devices, the DigniCap and Paxman scalp hypothermia systems, are now US Food and Drug Administration (FDA) cleared based on two prospective clinical trials in patients receiving (neo)adjuvant chemotherapy for breast cancer. FDA clearance has been extended to cover patients with all solid tumors, and extensive data exist to support this use. Manual caps are also available, although the safety issues must be carefully considered in the absence of controlled studies in the United States for these devices. (See 'Available devices and mechanism of benefit' below.)

Patients considering scalp hypothermia should be counseled on the efficacy, side effects, time requirements, and cost. Efficacy is variable and dependent on the type and intensity of planned chemotherapy, with significantly less hair preservation in patients receiving anthracyclines compared with non-anthracycline-based regimens. These data, along with information about side effects and time requirements, are reviewed below. (See 'Efficacy and safety' below.)

Less than or equal to 50 percent of patients develop grade 2 (≥50 percent) alopecia when receiving anthracyclines. Conversely, more than 60 percent of patients receiving taxanes will develop grade 1 (≤50 percent) alopecia. In addition, there is a financial burden of scalp hypothermia that should be discussed with each patient, as well as the adverse events of cold intolerance, headaches, forehead pain, and lightheadedness.

Not all patients should use scalp hypothermia, and contraindications are based on lack of efficacy in specific situations, or concerns about safety in patients with various underlying diseases. (See

'Indications and contraindications' below.)

Available devices and mechanism of benefit — The mechanism of action of scalp hypothermia includes local vasoconstriction of blood vessels, resulting in reduced delivery of chemotherapy to the scalp, decreased follicle cell metabolic rate, and reduced cellular drug uptake [2,54-56].

Two primary approaches to scalp hypothermia are currently available: FDA-cleared automated systems that circulate coolant through cooling caps and maintain a constant temperature; and frozen gel caps (unregulated) that must be much colder than the automated system when applied to the scalp and are changed as they warm after approximately 30 minutes on the scalp (table 5). Automatic devices use a portable cooling unit that circulates a coolant in a flexible cap so that temperature is maintained within a narrow range. Cooling with gel caps requires a cooler with dry ice or a freezer (if available in the chemotherapy infusion center).

Regardless of the specific device that is used, cooling is started approximately 30 minutes before the chemotherapy infusion starts in order to allow gradual cooling of the scalp to the desired temperature. Cooling is maintained for a period of time after the end of the chemotherapy infusion, generally at least 90 minutes and as long as three to four hours in some cases [57,58]. The duration of postinfusion cooling is determined at least in part by the clearance of high levels of chemotherapy, but also by the severity of the expected alopecia. Generally, an insulating cap is placed over the cold cap, and a protective covering is placed over the head between the scalp and cold cap. For most devices, caps are available in various sizes to be fitted to the patient's specific head size. A new device from Dignitana ("Delta") provides a cap that can be shaped to the individual head (similar to the design of the frozen Penguin cap, but with an automated circulating coolant); the efficacy of this design is being evaluated.

The optimal scalp temperature for successful cooling is thought to be 22ºC, although data regarding this specific number are quite limited, and it is difficult to accurately measure. Indeed, others attribute therapeutic success to obtaining a subcutaneous scalp temperature below 15ºC [59]. However, the caps themselves must be much colder in order to bring the scalp to the desired temperature. The type of cooling device determines the temperature, as manual caps must be much colder when initially applied to the scalp to account for their gradual increase in temperature before a new cap is applied. The automated units are usually set around 0°C.

Efficacy and safety — Scalp hypothermia has been used in more than 30 countries to prevent or reduce chemotherapy-induced alopecia, with variable success reported depending on the specific cooling device and type of chemotherapy [60,61]. In general, cooling has been less effective when used with combination anthracycline-containing chemotherapy regimens, although this is dependent

on dose and schedule [33,34,62-65]. Scalp cooling is now listed as an option for alopecia prevention in the National Comprehensive Cancer Network (NCCN) guidelines for breast cancer [66].

A meta-analysis in 2015 concluded that scalp hypothermia was the only intervention that significantly reduced the risk of chemotherapy-induced alopecia (10 studies, involving 818 patients and including three randomized trials; relative risk 0.38 compared with no cooling, 95% CI 0.32-0.45) [61]. No significant adverse events associated with scalp hypothermia were reported in this meta-analysis, although the reported studies did not always track toxicity. Although a subgroup analysis suggested a similar degree of efficacy for scalp hypothermia regardless of the underlying cancer, the majority of patients included in the meta-analysis had breast cancer, and most of the trials that included other patients did not provide detailed diagnoses.

These benefits have been confirmed in three more recent prospective trials evaluating the efficacy of two scalp hypothermia devices in women with early stage breast cancer [67-69]:

- In one multicenter, prospective cohort study, 101 patients with early stage breast cancer receiving non-anthracycline taxane-based chemotherapy who used the DigniCap scalp cooling device were compared with 16 concurrently treated controls who did not use the cooling device [67]. Alopecia was measured using the Dean Scale, with success defined as alopecia of 50 percent or less (Dean score 0 to 2 (table 3)) one month after the last chemotherapy infusion, and was graded by the patients themselves using photographs compared with their own baseline hair.

  The rate of significant alopecia (>2 on the Dean Scale) was 50 percent or less in 66.3 percent of the intervention group compared with none of the control group ($p<0.001$). Three of five quality of life measures were significantly better one month after the end of chemotherapy, including perception of hair loss, feeling upset over hair loss, and feeling less physically attractive as a result of the disease or its treatment. The primary toxicity was mild headache, and three patients stopped cooling due to feeling cold.

- A second trial randomly assigned 182 patients in a 2 to 1 ratio to use of the Paxman scalp cooling device or no scalp hypothermia during chemotherapy for breast cancer; 36 percent received anthracycline-based chemotherapy, while the remainder received a taxane, either alone or in combination with carboplatin, cyclophosphamide, pertuzumab, and/or trastuzumab [68]. Successful hair preservation was defined as less than 50 percent hair loss not requiring a wig, using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) criteria (grade 0 to 1 (table 1)), and was graded by a clinician unaware of treatment assignment at the end of four cycles of chemotherapy.

The interim analysis included 142 participants evaluable for the alopecia endpoint; all had completed four cycles of their assigned chemotherapy. Scalp hypothermia was graded as successful in 50.5 percent of patients compared with none of the control group (p = 0.0061). Adverse events were all grade 1 and 2, including primarily headache and feeling cold. Interestingly, in this study, there were substantial differences in the success of cooling by site and by drug group. An exploratory post hoc analysis indicated that only 16 percent of patients receiving anthracycline-based chemotherapy met criteria for success, compared with 59 percent of those receiving taxanes, although the confidence intervals were very wide. Seven patients discontinued cooling early, primarily due to feeling cold.

- The most recent published study evaluated the use of DigniCap in 139 patients with early stage breast cancer receiving adjuvant chemotherapy for their breast cancer [69]. The majority (95 percent) received at least four cycles of anthracycline-based chemotherapy (eribulin and cyclophosphamide), and many then received sequential taxanes. Using the Dean Scale (with success defined as a self-assessed score of <2), three weeks after completing all chemotherapy, 131 patients were evaluable for efficacy. Overall, 56 of the 131 patients reported success, for a rate of 43 percent. When evaluating the 104 patients who completed scalp cooling with all chemotherapy sessions, the success rate was higher at 54 percent. Overall, cooling was well tolerated, with nine patients discontinuing treatment due to adverse events. Although this study did meet its endpoint of success in 55 percent of patients, 43 percent of patients lost less than 50 percent of their hair, which may be acceptable to some patients. It is hoped that improved cap designs will improve the success with scalp cooling in patients treated with automated devices.

Scalp hypothermia using either the DigniCap or Paxman automated device is now available in a number of centers in the United States and around the world. For the frozen gel caps, generally patients must arrange to freeze the caps ahead of their infusion, then transport and store them in a cooler with dry ice. In addition, there must be someone accompanying the patient who can change the cap every 30 minutes. These gel caps are generally stored in the refrigerator until they need to be frozen again before the next chemotherapy session.

Adverse events from scalp hypothermia are generally mild and include patient discomfort from feeling cold, headache, nausea, dry skin, and claustrophobia. The manual caps have been reported to cause scalp thermal injury, which can probably be avoided by using an inner protective cap [67,68,70-75]. It has been suggested that use of scalp hypothermia may result in faster regrowth of hair following the end of chemotherapy [76]. Although this is not well documented, certainly retaining some hair at the end of chemotherapy could simply be associated with a shorter time to having an "acceptable" density of hair. A retrospective study in Spain including 492 patients who received docetaxel as adjuvant therapy for early stage breast cancer observed that fewer patients who had scalp cooling

during chemotherapy developed persistent chemotherapy-induced alopecia when compared with uncooled contemporary and historical controls [53].

The cost of using scalp cooling varies depending on the number of cycles of chemotherapy and the type of cooling device used, but the average total cost for scalp hypothermia is estimated to range between USD $1500 and $3000 per patient depending on the number of treatment cycles [77]. In addition, there may be institutional costs associated with extra time in the chemotherapy infusion center and additional personnel costs. In the United States, scalp hypothermia is only partially covered by a very few health insurance companies, creating financial concerns and variable costs for patients. One philanthropic organization provides some financial assistance to those who cannot afford scalp hypothermia (hairtostay.org), but it is hoped that insurance coverage will change in the near future with the availability of newer efficacy and safety data [77,78].

Indications and contraindications — Scalp hypothermia has been used successfully in patients with a variety of solid tumors receiving chemotherapy regimens associated with a high risk of complete alopecia, including breast, ovarian, and prostate cancers. In addition, patients with advanced cancer for whom alopecia represents an unacceptable toxicity from palliative chemotherapy that may significantly prolong life and quality of life may be offered the option of scalp hypothermia. However, the evidence for benefit is most robust in patients treated for breast cancer.

In terms of chemotherapy regimens, the success of scalp hypothermia is variable, particularly in patients receiving anthracycline-based combinations; overall, more than 50 percent of patients receiving anthracyclines in combination with cyclophosphamide develop complete or grade 2 alopecia. However, this may be acceptable to some patients, and the success may be very good in a minority. In addition, it is hoped that new designs with better-fitting caps will improve the success of scalp cooling with anthracycline-based combination chemotherapy.

Previously, some investigators have raised concerns regarding the possibility of increasing the risk of scalp metastasis in patients who have used scalp hypothermia [2,3,54,55,70,79-82]. The incidence of scalp metastasis in patients who have used scalp hypothermia devices has been best studied in breast cancer, where the risk of scalp metastasis is very low, and these are often discovered either along with or following a diagnosis of systemic disease. In one study of 61 patients with breast cancer receiving chemotherapy who used cooling caps, only one patient with underlying liver dysfunction developed cutaneous scalp metastasis [54]. However, larger studies evaluating patients using scalp hypothermia during chemotherapy for early stage breast cancer have shown no association between use of a cooling device and the subsequent development of scalp metastases, and one large study showed no impact of scalp hypothermia on survival [82-84]. In one review, the incidence of scalp skin metastasis in breast cancer patients was comparable for scalp-cooled (0.04 to 1 percent) and non-scalp-cooled patients (0.03 to 3 percent) [83]. A systematic review and meta-analysis evaluated 1959

patients using scalp cooling devices over an estimated mean time frame of 43.1 months and 1238 patients who did not use a scalp cooling device over an estimated mean time frame of 87.4 months [82]. The incidence rate of scalp metastasis in the scalp cooling group versus the no scalp cooling group was 0.61 (95% CI 0.32-1.1 percent) versus 0.41 percent (95% CI 0.13-0.94 percent); p = 0.43. In the prospective DigniCap study described above, no patient has developed scalp metastases at a median follow-up of four years [67].

Scalp hypothermia is contraindicated in several situations. First, scalp cooling devices are not designed for pediatric patients, so they should not be used in this setting.

Patients with solid tumors receiving continuous-infusion chemotherapy regimens over one day or longer that result in alopecia, and those undergoing whole-brain or targeted brain irradiation are also not good candidates for scalp hypothermia due to the ineffectiveness of cooling in these situations [81,85,86].

Scalp hypothermia is contraindicated in patients with cold agglutinin disease, cryoglobulinemia, and posttraumatic cold dystrophy [60]. Scalp hypothermia may be less effective in patients with significant liver dysfunction due to delayed drug metabolism, thereby allowing persistence of therapeutic drug levels for a long duration of time and increasing the risk of alopecia.

Due largely to the lack of data and the high potential for metastasis to the scalp, scalp cooling is not recommended for patients with small cell or squamous lung cancer or with skin cancers, including melanoma, squamous cell carcinoma, or Merkel cell carcinoma. Scalp cooling is contraindicated in patients with hematologic malignancies, including leukemia and some forms of lymphoma, and in those undergoing bone marrow or stem cell transplantation with myeloablative doses of chemotherapy and/or radiation therapy [87].

Pharmacologic interventions — Preclinical studies suggest that both small molecules and biologic agents may reduce or prevent alopecia by protecting the hair bulb from the damaging effects of chemotherapy. The only interventions tested in humans include topical bimatoprost, minoxidil, and calcitriol. At present, there are no pharmacologic interventions that have been approved by regulatory agencies for this indication.

Topical bimatoprost — Topical 0.03% bimatoprost, a prostaglandin analog, has been used successfully on the upper eyelid margin to enhance eyelash growth in patients with eyelash hypotrichosis. (See "Alopecia areata: Management", section on 'Eyelash loss'.)

Benefit for patients with chemotherapy-induced eyelid alopecia was observed in a randomized controlled trial of 130 patients with idiopathic or chemotherapy-induced alopecia [88]. Eligible patients had completed chemotherapy within 4 to 16 weeks with documented eyelash alopecia, and applied

one drop to the upper eyelid margin of each eye once daily. The primary endpoint of at least a one-grade improvement in investigator-assessed Global Eyelash Assessment (GEA) and at least a three-point improvement in patient-reported Eyelash Satisfaction Questionnaire (ESQ) domain 2 at month 4 was met in the chemotherapy group, with significantly less recovery in the control group (37.5 percent for bimatoprost versus 18.2 percent for vehicle), and benefits were more pronounced at month 12.

While topical bimatoprost could be considered for the **treatment** of chemotherapy-induced eyelash alopecia, there are no data supporting a preventive benefit, and safety during chemotherapy has not be evaluated.

Topical minoxidil — Minoxidil is thought to modify the hair cycle by prolonging the anagen phase. It may also increase hair follicle size, thereby counteracting miniaturization of the hair follicle, which is the characteristic histologic finding of androgenetic alopecia. Minoxidil has been FDA cleared for the treatment of androgenetic alopecia, and it has been used in women with endocrine therapy-induced alopecia, although efficacy data are limited. (See "Androgenetic alopecia in men: Pathogenesis, clinical features, and diagnosis", section on 'Pathogenesis' and "Female pattern hair loss (androgenetic alopecia in women): Pathogenesis, clinical features, and diagnosis" and "Female pattern hair loss (androgenetic alopecia in women): Treatment and prognosis" and "Treatment of androgenetic alopecia in men".)

Two randomized trials suggest that the effects of minoxidil in preventing or treating chemotherapy-induced alopecia are limited, at best:

- In a randomized trial of 48 patients with varying solid tumors receiving doxorubicin-containing regimens, topical minoxidil (2 percent solution applied twice daily) did not prevent the development of severe alopecia compared with placebo [89].
- A second trial in 22 women receiving chemotherapy after surgery for breast cancer also found that treatment with topical minoxidil did not prevent alopecia, but it did shorten the time to maximal regrowth and the time from maximal alopecia to first regrowth, and lengthened the time to maximal alopecia [90].

Finasteride — Finasteride, a type II 5-alpha-reductase inhibitor, is approved for the treatment of benign prostatic hyperplasia to improve symptoms, to reduce the risk of acute urinary retention or the need for surgical procedures, and to treat male pattern hair loss. There are limited data on its efficacy in women with female pattern alopecia, with variable success. Finasteride is not recommended for the treatment or prevention of alopecia in patients receiving chemotherapy, or in women with breast cancer and endocrine therapy-associated alopecia, due to safety concerns, as the drug has been shown to increase serum estrogen levels in 34 percent of patients [91] and has been associated with male gynecomastia.

Spironolactone — Spironolactone has been used to treat women with alopecia, with limited but clear efficacy in some patients [22,50,91-94]. Concern has been raised about the potential for increased estrogen levels with spironolactone, but this has not been consistently shown, and an analysis of three studies totaling 49,298 patients suggested that there is no increased risk of female breast cancer while on spironolactone for alopecia [91]. (See "Treatment of androgenetic alopecia in men" and "Female pattern hair loss (androgenetic alopecia in women): Treatment and prognosis".)

Topical calcitriol — Pretreatment with topical calcitriol (1,25(OH)2D3; the most active metabolite of vitamin D) protects rats from cyclophosphamide-, etoposide-, and doxorubicin-induced alopecia [95]. Effects may be mediated by direct biological activity or modulation of other factors. Specific receptors for calcitriol are present in rat, murine, and human skin cells, and calcitriol induces differentiation of murine epidermal keratinocytes. When human cultured keratinocytes are incubated with calcitriol, there is a dose- and time-dependent stimulation of differentiation and inhibition of DNA synthesis.

One study found that pretreatment with calcitriol did not alter the cytotoxic effects of the chemotherapy but did prevent significant alopecia [96]. However, a phase I trial of 12 patients receiving anthracycline- and cyclophosphamide-containing chemotherapy for breast cancer failed to demonstrate any benefit in preventing chemotherapy-induced alopecia [97]. Furthermore, concerns about potential protection of the cancer cells from the effects of chemotherapy have been raised [95,96,98]. This treatment is not recommended for prevention of chemotherapy-induced alopecia.

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient education: Hair loss from cancer treatment (The Basics)")

SUMMARY AND RECOMMENDATIONS

- Alopecia is a transient and usually (although not always) completely reversible consequence of systemic cancer therapy that can be psychologically devastating. A wide range of chemotherapy agents can affect the growing cells of the hair follicle. The frequency and severity of alopecia vary depending on the specific chemotherapy agent or combination regimen administered (table 4), the dose of the drugs, and the treatment schedule. The majority of chemotherapy-induced alopecia is reversible once therapy is discontinued, with the possible exception of some molecularly targeted therapies. (See 'Effects of chemotherapy' above.)

- Alopecia is generally most prominent on the scalp, and there is a predilection for areas that show low total hair densities, in particular the crown and vertex. All patients who will receive chemotherapy that may result in alopecia should be informed of the side effect of alopecia. Options such as scalp hypothermia head wraps, hats, or wigs should be discussed in advance so that the patient can be more physically and emotionally prepared. For patients who are receiving docetaxel, it is important to advise about the risk of prolonged or permanent alopecia. (See 'Clinical characteristics' above and 'Recovery and reversibility' above.)

- Scalp hypothermia minimizes delivery of chemotherapeutic agents to the scalp and reduces metabolism of the hair follicle cell, thereby decreasing the risk of alopecia. Prospective studies in breast cancer confirm that several devices can reduce or prevent alopecia in a majority of patients receiving taxane-based chemotherapy, with lower success rates seen in those receiving anthracycline-based regimens. Although previous concerns arose regarding the potential risk of scalp metastasis, newer studies and a review of all the available published data have failed to substantiate this concern. (See 'Scalp hypothermia (scalp cooling)' above.)

  For patients with solid tumors who are receiving chemotherapy that is expected to result in significant alopecia, it is reasonable to consider the use of an automated scalp hypothermia device, where available. Two such devices, the DigniCap and Paxman scalp hypothermia systems, have been used extensively outside of the United States, and both are now also US Food and Drug Administration (FDA) cleared in the United States for this use. Manual caps are also available, although these caps are unregulated, and there are risks associated with their use. (See 'Available devices and mechanism of benefit' above.)

  Patients considering scalp hypothermia should be counseled on the variable success of this approach. In particular, rates of success in patients receiving anthracycline-based combination therapy are highly variable, and overall, less than 50 percent of patients keep at least 50 percent of their hair. In addition, there is a financial burden of scalp hypothermia that should be discussed with each patient, as well as the adverse events of cold intolerance, headaches, forehead pain,

and lightheadedness. New caps are being developed or are now available that have improved the fit of the cap to the skull. It is hoped that these new caps will improve the efficacy of scalp hypothermia in patients receiving anthracycline-based chemotherapy. (See 'Efficacy and safety' above.)

Scalp hypothermia is contraindicated or is unlikely to be effective in patients with specific underlying diseases or in those receiving radiation therapy to the brain or high doses of chemotherapy with bone marrow or stem cell rescue.

We do not discuss the option of scalp hypothermia with patients with diseases associated with high levels of circulating tumor cells, such as leukemia and some types of lymphoma. Scalp hypothermia is contraindicated in patients with cold agglutinin disease, cryoglobulinemia, and posttraumatic cold dystrophy, and it should be used with caution in patients with liver dysfunction. (See 'Indications and contraindications' above.)

- Preliminary studies suggest that a variety of both small molecules and biologic agents may reduce or prevent alopecia by protecting the hair bulb from the damaging effects of chemotherapy. However, to date, there are no specific pharmacologic interventions that have demonstrated consistent enough activity in randomized trials in humans to justify their general use to prevent chemotherapy-induced alopecia. (See 'Pharmacologic interventions' above.)

  While topical bimatoprost could be considered for the treatment of chemotherapy-induced eyelash alopecia, there are no data supporting a preventive benefit. (See 'Topical bimatoprost' above.)

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